Exhibit A

The opinion in support of the decision being entered today was not written for publication and is not binding precedent of the Board.

Paper No. 18

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Ex parte WILLIAM G. WEISBURG and DALE A. PELLETIER

Appeal No. 1999-2550
Application 08/452,129

ON BRIEF

Before ADAMS, MILLS, and GRIMES, Administrative Patent Judges.

GRIMES, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. § 134 from the examiner's final rejection of claims 5, 6, 12-14, 18, 19, and 21-31, all of the claims remaining.

Claims 14 and 18 are representative and read as follows:

14. A method for detecting Mycoplasma hominis, Ureaplasma urealyticum, or Mycoplasma genitalium in a sample comprising:

    a) contacting said sample with at least one nucleic acid composition having 10 to 250 nucleotides which, under conditions that allow said nucleic acid composition to hybridize, hybridize preferentially, to rRNA or rDNA of said mycoplasma organism,

b) imposing hybridization conditions on said sample to form a hybridization product in the presence of target; and,

c) detecting said hybridization product as an indication of the presence of said mycoplasma.

18. A kit for detecting the presence of one or more of the following organisms consisting of Mycoplasma hominis, Ureaplasma urealyticum and Mycoplasma genitalium, comprising nucleic acids having 10 to 250 nucleotides capable of hybridizing to rRNA or rDNA of said organisms in preference to rRNA or rDNA of humans, fungi and other Mycoplasma wherein said nucleic acids are complementary or homologous to at least one region of rRNA or rDNA selected from the group of regions consisting of positions 50 to 100, 425 to 485, or 1100 to 1150 of Mycoplasma hominis 16S rRNA, positions 50 to 100, 150 to 250, 425 to 485, 800 to 850, 1090 to 1160, and 1220 to 1260 of Ureaplasma urealyticum 16S rRNA, positions 1110 to 1160 of Mycoplasma genitalium 16S rRNA, and positions 260 to 330, 1590 to 1630, and 1850 to 1900 of Mycoplasma genitalium 23S rRNA and such numerical designations are nucleotide positions counted from the 5' end of the RNA molecule.

The examiner relies on the following references:

Gobel et al (Gobel) "Oligonucleotide Probes Complementary to Variable Regions of Ribosomal RNA Discriminate between Mycoplasma Species," Journal of General Microbiology, Vol. 133, pp. 1969-1974 (1987)

Weisburg et al. (Weisburg) "A Phylogenetic Analysis of the Mycoplasmas: Basis for Their Classification," Journal of Bacteriology, Vol. 171, No. 12, pp. 6455-6467 (1989)

Joklik et al. (eds.), "Zinsser Microbiology", 18th ed., Appleton-Century Crofts, Norwalk, CT, p. 794 (1984)

Claims 5, 6, 12-14, 18, 19, and 21-31 stand rejected under 35 U.S.C. § 112, first paragraph, as unsupported by an enabling disclosure

Claims 14, 18, 19, 21, 22, 25, and 26 stand rejected under 35 U.S.C. § 103 as obvious in view of Gobel and Weisburg.

We reverse the rejection for non-enablement but affirm the rejection for obviousness.

Background

"Mycoplasmas are small wall-less bacteria, primarily isolated from animal sources including humans." Specification, page 1. "Among the mycoplasmas known to be pathogenic, Mycoplasma pneumoniae is historically the most well studied, it is the major infectious agent of primary atypical pneumonia." Id. "Three other mycoplasma species, which can be isolated from the human genito-urinary tract, Mycoplasma hominis, Mycoplasma genitalium and Ureaplasma urealyticum, are somewhat more enigmatic in the clinical implications of the detection of these organisms in the human body." Id., page 2. These three species are collectively referred to as "genital mycoplasmas," id., and are "believed to be the cause of nongonococcal urethritis, pelvic inflammatory diseases, septic abortion, and a wide array of diseases of other tissues." Id., page 1.

The specification discloses a method of identifying and distinguishing between M. hominis, M. genitalium, and U. urealyticum. The disclosed method is based on hybridization of bacterial ribosomal RNA (rRNA) or ribosomal DNA (rDNA) with probes based on regions of the 16S and 23S rRNA molecules of the genital mycoplasmas. See page 7. This method, and the probes used therein, are the subject of the claims on appeal.

Discussion

1. The non-enablement rejection

The examiner rejected all of the claims as being broader than the enabling scope of the disclosure. He stated that

> insufficient information is presented in the specification to identify 10-mers or even larger sequences which would be functional in a specific detection assay. There are no working examples in the specification of sequences which would be used for this specific detection other than the probes explicitly listed, the minimum size of which is 31 nucleotides. . . . It is extremely unpredictable to identify which 10-mers or larger sequences from the mycoplasma sequence would distinguish between mycoplasmas and host or between different mycoplasma species. . . . The quantity of experimentation that would be necessary to identify functional sequences is substantial, given the lack of information in the specification and prior art and the extreme unpredictability of the art. Sequencing of each organism whose exclusion was desired, along with synthesis and characterization of each probe would be necessary. Accordingly, undue experimentation is required to make and use the invention as broadly claimed.

Examiner's Answer, pages 4-5. The examiner concluded that the claims are enabled "only for claims limited to the specific sequences disclosed in the specification." Id., page 3.

"When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application." In re Wright, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993). "Enablement is a legal determination of whether a patent enables one skilled in the art to make and use the claimed

invention, [and] is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive." Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1987) (citation omitted). "The key word is 'undue,' not 'experimentation.'" In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976).

In this case, the examiner appears to be demanding a degree of guidance that would allow those skilled in the art to determine without any experimentation whether a given probe would hybridize specifically to one species of mycoplasma. See the Examiner's Answer, page 5 ("Sequencing of each organism whose exclusion was desired, along with synthesis and characterization of each probe would be necessary."). This degree of guidance is beyond what is demanded by 35 U.S.C. § 112, first paragraph. See Hybritech, 802 F.2d at 1384, 231 USPQ at 94 ("Enablement . . . is not precluded even if some experimentation is necessary, although the amount of experimentation needed must not be unduly extensive.").

The instant specification provides sixteen probes that correspond to regions of the mycoplasma 16S rRNA (see pages 23-25). The specification also discloses the method by which these specific probes were derived. First, the nucleotide sequences of M. genitalium 16S and 23S rRNAs "were determined by standard laboratory protocols." Page 13. Then the sequences of 16S and 23S rRNAs from M. genitalium, M. hominis, and U. urealyticum were precisely aligned, together with "homologous sequences of other mycoplasma and

nonmycoplasma ribosomal RNA sequences in order to identify regions of interesting variation." Id. The specification discloses the other organisms used in the rRNA sequence alignment and also discloses that the rRNA sequences used are publicly available. See id., pages 13-14.

Thus, the specification discloses all of the data and methods used to derive the specifically disclosed probes. The examiner has not adequately explained why this guidance is inadequate to enable a person of ordinary skill in the art to follow the disclosed probe development strategy—using the disclosed rRNA sequences and determining, if necessary, any additional sequences by standard laboratory techniques—to identify other regions of the mycoplasma rRNA sequences that would be useful as species-specific probes. Therefore, we reverse the rejection under 35 U.S.C. § 112, first paragraph.

2. The obviousness rejection

The examiner rejected claims 14, 18, 19, 21, 22, 25, and 26 under 35 U.S.C. § 103. These claims stand or fall together because Appellants have not stated that they stand or fall separately, nor have Appellants provided any separate arguments. See 37 CFR § 1.192(c)(7); In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983) ("Since the claims are not separately argued, they all stand or fall together."). Therefore, we will limit our analysis to claim 14, the broadest claim subject to this rejection.

Claim 14 is directed to a method of detecting M. hominis, M. genitalium, or U. urealyticum by contacting a sample with a probe having 10-250 nucleotides which hybridizes preferentially to the rRNA or rDNA of the targeted mycoplasma

species, hybridizing the probe to the rRNA or rDNA in the sample, and detecting the resulting hybridization product. The examiner rejected the claimed method as obvious over Gobel and Weisburg. As noted by the examiner, Gobel teaches a method for detecting Mycoplasma species and distinguishing between various species of Mycoplasma, based on hybridization of probes complementary to sequences of 16S rRNA. In particular, Gobel teaches that a probe (MP20) corresponding to positions 458-477 of the 16S rRNA hybridized to the rRNA of the source species (M. pneumoniae) but not to other species of mycoplasma. Pages 1970-1971. Gobel teaches that MP20 was able to distinguish between even "closely related" mycoplasma species. Page 1971. Gobel does not teach probes corresponding to rRNA sequences from any of the mycoplasma species recited in the instant claims (M. hominis, M. genitalium, or U. urealyticum).

The examiner found this deficiency to be remedied by Weisburg, who "teaches the entire 16S rRNA sequences of a variety of Mycoplasma including Mycoplasma hominis . . . and Ureaplasma urealyticum." Examiner's Answer, page 6. Thus, he concluded, "[i]t would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the method of Gobel with the sequence of Weisburg since Gobel states 'These observations indicated that it might be possible to construct species-specific probes based on synthetic oligonucleotides complementary to highly variable sequences in the 16S rRNA (page 1969, subheading "Introduction").'" Id., pages 6-7.

We agree with the examiner's conclusion. The cited references would have provided both motivation to combine their respective teachings and a reasonable expectation of success. In particular, Gobel teaches that the disclosed 16S rRNA hybridization assay "may easily be adapted for the detection or identification of other bacterial species." Pages 1972-1973. Gobel also suggests that the properties of the disclosed assay make it particularly suitable for use in diagnosis. See page 1973:

> [The assay] combines three attributes of importance to a wide variety of diagnostic applications. (1) A range of probes, varying in specificity from very narrow (as described here) to very wide, can be selected from appropriate domains of the bacterial 16S or 23S rRNA. . . . (2) The high number of rRNA target molecules results in a sensitivity at least 100 times greater than that of bacterial DNA targets. . . . (3) The use of short probes substantially reduces hybridization times.

In addition, Appellants have admitted that "Mycoplasma hominis has been implicated as a causative agent of salpingitis, amnionitis, nonspecific vaginitis, and postpartum septic fever. . . . Ureaplasma urealyticum has been implicated in nongonococcal urethritis, chorioamnionitis, premature delivery, and perinatal morbidity and mortality." Specification, pages 2-3. These disclosures would have motivated those skilled in the art to combine the diagnostic assay disclosed by Gobel with the M. hominis and U. urealyticum 16S rRNA sequences disclosed by Weisburg, in order to identify infections by those mycoplasma species. Thus, the claimed invention would have been prima facie obvious to those of ordinary skill in the art.

"After a prima facie case of obviousness has been established, the burden of going forward shifts to the applicant. Rebuttal is merely a 'showing of facts supporting the opposite conclusion,' and may relate to any of the Graham factors including so-called secondary considerations." In re Piasecki, 745 F.2d 1468, 1472, 223 USPQ 785, 788 (Fed. Cir. 1984) (citations omitted). "The patent applicant may . . . attack the Examiner's prima facie determination as improperly made out, or the applicant may present objective evidence tending to support a conclusion of nonobviousness." In re Fritch, 972 F.2d 1260, 1265, 23 USPQ2d 1780, 1783 (Fed. Cir. 1992)

In this case, Appellants argue that "there is no guidance on selecting the target areas recited in the instant claims, which Applicants have found are operable." Appeal Brief, page 5. Appellants argue that, even if the probe disclosed by Gobel (corresponding to positions 458-478) is within the region recited in the claims (positions 425-485), "Gobel et al.'s probes failed to hybridize to M. hominis and Ureaplasma urealyticum 960 among others." Id.

This argument is not persuasive. As we understand it, Appellants' argument is that those skilled in the art would have been led away from Gobel's MP20 probe because the probe hybridized only to M. pneumoniae rRNA and not to rRNA of other mycoplasma species. We disagree. The species-specificity of the probes is touted by Gobel as an advantage of the disclosed probes, not a drawback. See page 1969, the abstract ("This test is a most sensitive assay for species-specific detection of bacteria."); page 1971 ("The probe MP30, unexpectedly, cross-hybridized with DNA from M. genitalium, a mycoplasma

which is closely related to M. pneumoniae. . . . MP20, however, was able to discriminate between both species."). That is, the ability of the probe to distinguish M. pneumoniae from even closely related species such as M. genitalium shows the accuracy of the probes in identifying the targeted mycoplasma species. Thus, far from leading those skilled in the art away from the claimed invention, the feature emphasized by Appellants would actually have been considered an advantage by those skilled in the art.

Appellants also argue that "one cannot slavishly say that Applicant's [sic] invention is negated by hypothetically using Gobel's teachings to modify Gobel's probes and use such modified probes in some indeterminable target area of Weisburg et al[.] merely because Weisburg teaches the entire 16S rRNA of some Mycoplasmas." Brief, page 6.

This argument is also not persuasive, because it is not an accurate reflection of the examiner's position or the teachings of the prior art. As discussed in detail above, the prior art discloses a particular region of mycoplasma 16S rRNA that is suitable for species-specific hybridization assays, discloses the appropriate sequences of the 16S rRNAs from M. hominis and U. urealyticum, and provides both motivation and a reasonable expectation of success in combining those teachings. The prior art therefore renders the instant claims prima facie obvious. Since Appellants have not effectively rebutted the examiner's prima facie case of obviousness, we affirm the rejection under 35 U.S.C. § 103.

Other Issues

The instant application is disclosed to be a divisional of application 07/673,661, which issued as U.S. Patent 5,843,667. The claims of the '667 patent are directed to probes and hybridization methods similar to those of the instant claims, but are limited to specific probes. The claims of the '667 patent thus appear to be species or subgenera encompassed by the more generic claims of the instant application. In such cases, where the species and the genus are not patentably distinct, a rejection for obviousness-type double patenting is appropriate. See In re Goodman, 11 F.3d 1046, 1053, 29 USPQ2d 2010, 2016 (Fed. Cir. 1993):

> By adopting the easy course of filing a continuation or divisional application to gain a narrow claim, a patentee could gain an extension of the term on a species when the broad genus later issued. This practice would extend the exclusionary right past the 17-year limit mandated by Congress. . . . A second application—"containing a broader claim, more generical in its character than the specific claim in the prior patent"—typically cannot support an independent valid patent.
>
> [The application claims] are generic to the species of invention covered by claim 3 of the patent. Thus, the generic invention is 'anticipated' by the species of the patented invention. This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generic application.

(Citations and footnote omitted).

This issue does not appear to have been addressed in this case on the record. Upon return of this application, the examiner should consider whether a rejection for obviousness-type double patenting would be appropriate.

Summary

We affirm the rejection under 35 U.S.C. § 103 because the cited references support a prima facie case of obviousness, which has not been effectively rebutted. However, we reverse the rejection for nonenablement. Therefore, claims 5, 6, 12, 13, 23, 24, and 27-31 are not subject to any outstanding rejection, although the examiner should consider whether, in the absence of a terminal disclaimer, they should be rejected for obviousness-type double patenting.

AFFIRMED IN PART

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